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A CONVENIENT METHOD FOR THE SYNTHESIS OF 2,3-DIOXO-1,2,3,4-TETRAHYDROQUINOXALINES

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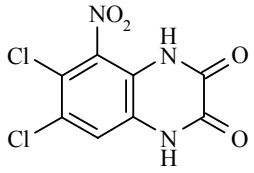
A method for the synthesis of substituted 2,3-dioxo-1,2,3,4-tetrahydroquinoxalines by the reduction of substituted (o-nitrophenyl)glycines with subsequent oxidation of the 2-oxo-1,2,3,4-tetrahydroquinoxaline products has been developed. When tin(II) chloride was used as the reducing agent a chlorine atom was introduced ortho to the NHC(O) fragment of the heterocycle.

Keywords: 2,3-dioxo-1,2,3,4-tetrahydroquinoxaline-5-carboxylic acid, 2,3-dioxo-1,2,3,4-tetrahydroquinoxaline-6-carboxylic acid, substituted (*o*-nitrophenyl)glycine, reductive cyclization.

With the objective of finding biologically active substances with structures similar to the known material ACEA-1021 (**1**), Kornberg et al [1] synthesized a substituted 2,3-dioxo-1,2,3,4-tetrahydroquinoxaline in which a carbamoyl group was present in place of the electron-withdrawing nitro group. One of the intermediate products in this scheme is methyl 6-methyl-7-nitro-2,3-dioxo-1,2,3,4-tetrahydroquinoxaline-5-carboxylate (**2**).



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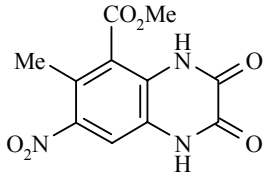

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For the synthesis of this heterocycle a complex multistep route was proposed, the possibility of which was limited by the presence of a methyl group in the 2-amino-6-methylbenzoic acid starting material. We have developed a simpler and universal method for the synthesis of analogous compounds based on 2-chloro-3,5-dinitrobenzoic acid. Methyl 8-chloro-7-nitro-2,3-dioxo- (**3**) and 7-nitro-2,3-dioxo-1,2,3,4-tetrahydroquinoxaline-5-carboxylates (**4**) were synthesized as follows:

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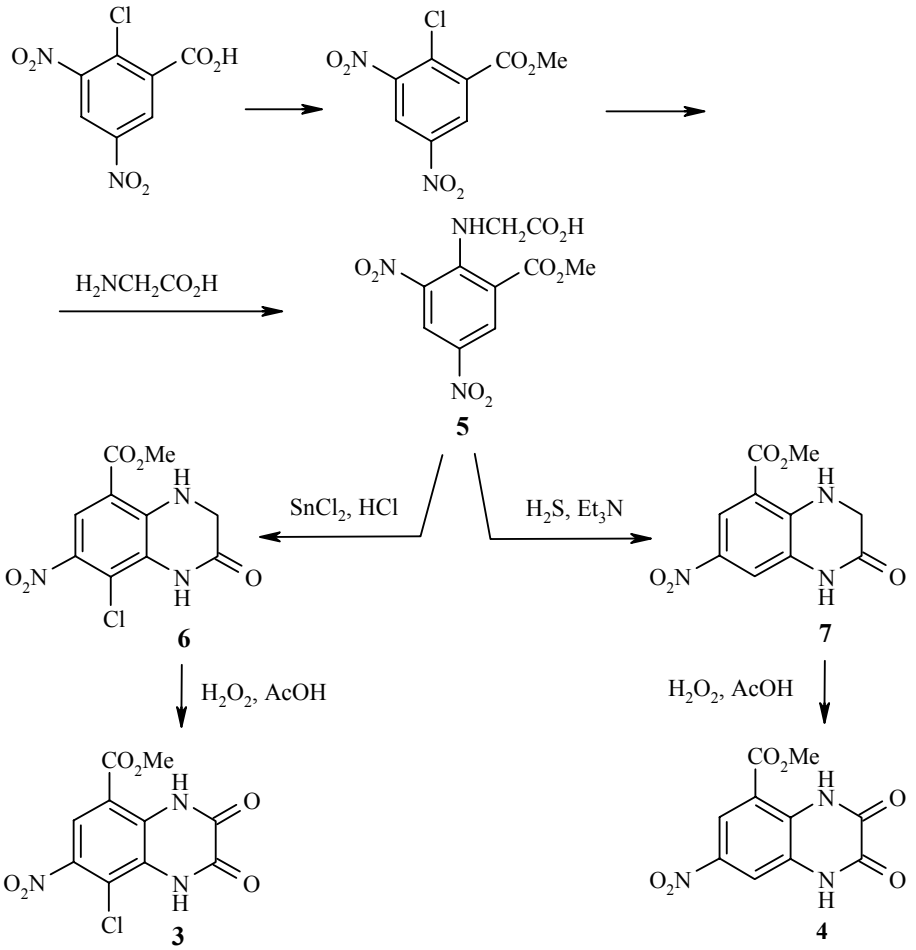
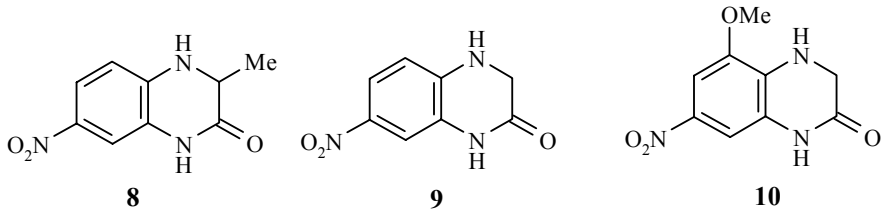


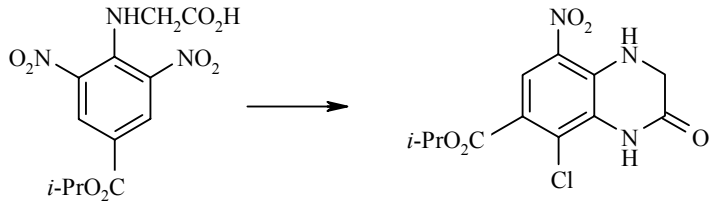
The reductive cyclization of N-(6-methoxycarbonyl-2,4-dinitrophenyl)glycine (**5**) deserves particular attention. Previously [2] the synthesis of 3-methyl-7-nitro- (**8**), 7-nitro- (**9**) and 5-methoxy-7-nitro-2-oxo-1,2,3,4-tetrahydroquinoxaline (**10**) by the reduction of the corresponding substituted (*o*-nitrophenyl)glycines was reported..



In the first case ammonium sulfide was used as the reducing agent and the reaction occurred readily and unambiguously. In our work the best results were obtained in the reduction of compound **5** with hydrogen sulfide in the presence of triethylamine. Our results were different from those reported in [2] when tin(II) chloride was used as the reducing agent.

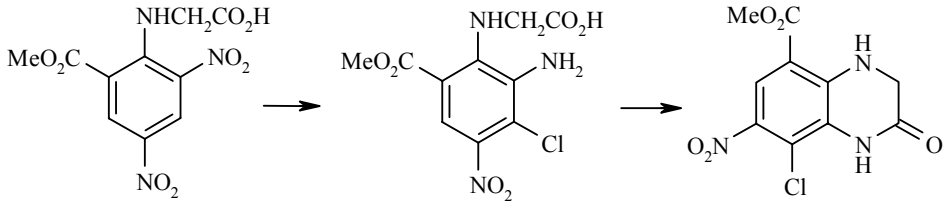
Horner et al [2] carried out the reduction of the corresponding substituted (*o*-nitrophenyl)glycine in ethanol saturated with HCl and obtained satisfactorily high yields of compounds **9** and **10**. Under the same conditions we obtained the chlorine-containing compound **6**. Introduction of a chlorine atom into an aromatic ring is not a rare phenomenon in the reduction of a nitro compound with tin(II) chloride, which is facilitated by

a high temperature and a high concentration of HCl. This is explained by the intermediate formation of an arylhydroxylamine and its subsequent rearrangement [3, 4]. We turn our attention to the fact that during the synthesis of compound **6** the chlorine atom does not enter the *para* position, as is normally observed [3], but into the position *ortho* to the amino group formed. The same was observed in the reduction of N-(4-isopropylcarboxyl-2,6-dinitrophenyl)glycine (**11**) with tin(II) chloride in isopropanol saturated with HCl which gave isopropyl 5-chloro-8-nitro-3-oxo-1,2,3,4-tetrahydroquinoxaline-6-carboxylate (**12**).



11 **12**

It is most likely that this orientation is connected to the electron–withdrawing nitro- and alkoxycarboxyl groups, but a steric factor is not excluded. We propose the following scheme for the cyclization:



In the first step reduction of a nitro group is accompanied by chlorination while in the second step intramolecular acylation occurs which leads to the closing of the 1,2,3,4-tetrahydroquinoxalin-2-one ring. The position of the chlorine in compounds **6** and **12** was determined by two-dimensional correlation NOESY spectra. The signal corresponding to the interaction of the proton of the NHC(O) unit with the neighboring proton of the aromatic ring, which is observed, for example in the spectrum of compound **7**, is absent from the spectra of compounds **6** and **12**. This is explained by the presence of a chlorine atom in the corresponding position of the aromatic ring. We used hydrogen peroxide in glacial acetic acid for the oxidation of compounds **6** and **7** into **3** and **4** respectively.

EXPERIMENTAL

^{1}H NMR spectra of DMSO-d_6 solutions with TMS as internal standard were recorded with a Bruker WP-200 (200 MHz) machine. Chromato mass spectroscopic investigations of isolated compounds were carried out with Hewlett Packard 6890 gas chromato-mass spectrometer with a 5973 mass spectromer detector, an HP-5MS column (30 m × 0.25 μm) with a 0.25 μm thich liquid phase, helium carrier gas (40 cm/s), a flow split of 20:1, source temperature 150°C, injector temperature 230°C, temperature gradient from 40 to 320°C (25°C/min), and EI ionization. Two-dimensional NOESY spectra were recorded with a Bruker DAX-500 at 30°C using a Bruker standard method.

Methyl 2-chloro-3,5-dinitrobenzoate and isopropyl 4-chloro-3,5-dinitrobenzoate were made by a standard method [5].

N-(6-Methoxycarbonyl-2,4-dinitrophenyl)glycine (5). A solution of Na_2CO_3 (4.6 g, 45.0 mmol) and glycine (2.2 g, 30.0 mmol) in water (20 ml) was added to a boiling solution of methyl 2-chloro-3,5-dinitrobenzoate (7.8 g, 30.0 mmol) in methanol (20 ml), the mixture was boiled for 20 min, cooled, acidified with 10% HCl, and the yellow precipitate was filtered off and recrystallized from methanol to give compound **5**, 4.4 g, (64%); mp 153-155°C.

N-(4-Isopropoxycarbonyl-2,6-dinitrophenyl)glycine (11) was obtained analogously from isopropyl 4-chloro-3,5-dinitrobenzoate in 2-propanol. Yield 93%; mp 177-179°C.

Methyl 8-Chloro-7-nitro-2-oxo-1,2,3,4-tetrahydroquinoxaline-5-carboxylate (6). A solution of $SnCl_2 \cdot 2H_2O$ (9.0 g, 40.0 mmol) in methanol (40 ml) saturated with HCl was added dropwise to a boiling solution of compound **5** (3.0 g, 10.0 mmol) in methanol (50 ml) saturated with HCl for 9 h. After cooling, the precipitate was filtered off and recrystallized from dilute acetic acid to give compound **6** (1.7 g, 60%) as yellow needles; mp 269-271°C. ^{1}H NMR spectrum, δ, ppm: 9.44 (1H, br. s, NH); 8.42 (1H, br. s, NH); 8.27 (1H, s, H_{arom}); 4.13 (2H, s, CH_2); 3.86 (3H, s, CH_3). Mass spectrum, *m/z*: 285, 287 [M^+]. Found, %: 45.25; H 2.98; N 15.80. $C_{10}H_8ClN_3O_5$. Calculated, %: C 45.20; H 3.01; N 15.82.

Methyl 7-Nitro-2-oxo-1,2,3,4-tetrahydroquinoxaline-5-carboxylate (7). Hydrogen sulfide (made by adding dilute HCl solution $Na_2S \cdot 9H_2O$ (8.0 g, 33.3 mmol) was passed through a solution of compound **5** (1.0 g, 3.3 mmol) and Et_3N (2.4 ml, 17.3 mmol) in water (20 ml) heated to 50°C. At the end of the reaction, the mixture was cooled, acidified with HCl solution, the yellow precipitate was filtered off, dissolved in glacial acetic acid, filtered from sulfur, diluted with water, and the precipitate filtered off. Recrystallization from dilute acetic acid gave compound **7** (0.2 g, 24%); mp <300°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.82 (1H, s, NH); 8.47 (1H, s, NH). 8.29 (1H, d, J = 2.76, H_{arom}); 7.66 (1H, d, J = 2.76, H_{arom}); 4.15 (2H, s, CH_2); 3.87 (3H, s, CH_3). Mass spectrum, *m/z*: 251 [M^+]. Found, %: C 45.25; H 2.98; N 15.80. $C_{10}H_9N_3O_5$. Calculated, %: C 45.40; H 3.01; N15.82.

Methyl 8-Chloro-7-nitro-2,3-dioxo-1,2,3,4-tetrahydroquinoxaline-5-carboxylate (3). A hot solution of compound **6** (0.8 g, 2.8 mmol) in glacial acetic acid (30 ml) was added to a mixture of glacial acetic acid (30 ml) and 50% H_2O_2 (2 ml) heated to 60°C, the mixture was heated to boiling and kept at that temperature for 30 min, the solvent was evaporated to 20 ml and diluted with water. The yellow-orange precipitate was filtered off and recrystallized from dilute acetic acid to give compound **3** (0.6 g, 76%); mp 284-286°C. ^{1}H NMR spectrum, δ, ppm: 11.52 (2H, br. s, NH); 8.32 (1H, s, H_{arom}); 3.97 (3H, s, CH_3). Mass spectrum, *m/z*: 299, 301 [M^+] . Found, %: C 40.05; H 2.00; N 14.04. $C_{10}H_6ClN_3O_6$. Calculated, %: C 40.07; H 2.00; N 14.02.

Methyl 7-Nitro-2,3-dioxo-1,2,3,4-tetrahydroquinoxaline-5-carboxylate (4) was prepared analogously. Yield 47%; mp 267-268°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.37 (1H, s, NH); 11.39 (1H, s, NH); 8.39 (1H, d, J = 2.30, H_{arom}); 8.14 (1H, d, J = 2.30, H_{arom}); 3.99 (3H, s, CH_3). Mass spectrum, *m/z*: 265 [M^+], Found, %: C 45.27; H 2.66; N 15.85. $C_{10}H_7N_3O_6$. Calculated, %: C 45.28; H 2.64; N 15.85.

Isopropyl 5-Chloro-8-nitro-3-oxo-1,2,3,4-tetrahydroquinoxaline-6-carboxylate (12). A boiling solution of compound **11** (0.5 g, 1.5 mmol) in 2-propanol (10 ml) was saturated with gaseous HCl for 35 min, a solution of $SnCl_2 \cdot 2H_2O$ (1.2 g, 4.7 mmol) in 2-propanol (10 ml) saturated with HCl was added dropwise while boiling, the mixture was cooled poured onto ice, acidified with 35% HCl solution, the orange precipitate was filtered off and recrystallized from dilute acetic acid to give compound **12**, (0.3 g, 63%); mp 193-195°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 9.10 (1H, s, NH); 8.45 (1H, s, NH); 8.29 (1H, s, H_{arom}); 5.20 (1H, t, J = 7.70, CH); 4.15 (2H, s, CH_2); 1.45 (6H, d, J = 7.70, 2 CH_3). Mass spectrum, *m/z*: 313, 315 [M^+]. Found, %: C 45.90; H 3.85; N 13.40. $C_{12}H_{12}ClN_3O_5$. Calculated, %: C 45.93; H 3.83; N 13.40.

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